Milrinone

By Alex Yartsev - 17/06/2015
Last updated 18/12/2023 - 18:10

This chapter is relevant to Section G7(i) of the 2023 CICM Primary Syllabus, which asks the exam candidate to *"understand the pharmacology of inotropes and vasopressors"*. The main focus here will be the differences between milrinone and dobutamine. These are the two major old-style inotropes in our arsenal, and there are situations that favour the use of one over the other. Moreover, in the First Part CICM exam, milrinone has so far appeared only twice, and each time the trainees were expected to compare it to something.

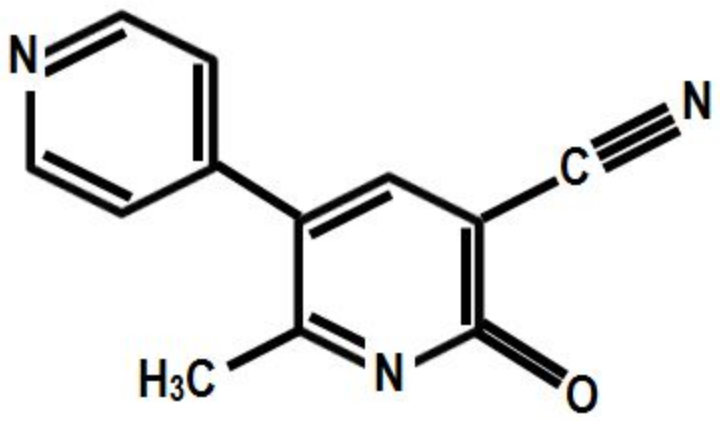
- Question 2 from the first paper of 2018 (adrenaline vs. milrinone)
- Question 14 from the second paper of 2011 (dobutamine vs. milrinone)

These have fortunately been limited to comparisons of milrinone with another drug, which should have the effect of limiting the expected level of detail (as it would be unreasonable to expect too much detail where the question-answering time for both drugs is limited to 10 minutes). As such, what follows is a fairly brief list of properties.

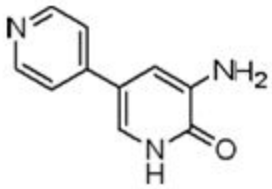
Class	Ino-dilator
Chemistry	Biperidine
Routes of administration	IV; but can also be administed as a nebulised aerosol, and had initially been marked as an oral preparation
Absorption	Well absorbed orally; 92% oral bioavailability
Solubility	pKa 4.6 and 8.5; good solublity at physiological pH
Distribution	0.38L/kg; 70% protein bound
Target receptor	Phosphodiesterase 3
Metabolism	Mostly cleared renally; of the free fraction some undergoes hepatic metabolism into an inactive o-glucouronide, and the rest is excreted unchanged at a rate which varies depending on renal blood flow
Elimination	Half life is 2.3 hours in patients with heart failure, slightly less in normal healthy adults and longer in patients with renal dysfunction
Time course of action	Onset of action is usually within 5-15minutes
Mechanism of action	Increases cyclic AMP by inhibiting phosphodiesterase 3, which is responsible for cAMP catabolism. Selective for vascular smooth muscle and cardiac muscle.
Clinical effects	Improved ventricular contractility; decreased systemic vascular resistance; decreased pulmonary vascular resistance; tachycardia; propensity to arrhythmias.

Single best reference for further information Canadian (Novopharm) product pamphlet for milrinone lactate

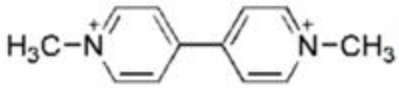
Chemical structure of milrinone, and its chemical relatives



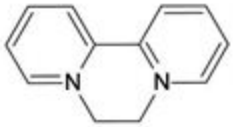
Milrinone is a bipyridine inotrope (or "ino-dilator" if you will), belonging to a class essentially of its own. Well, at least since Bedford laboratories ceased production of inamrinone in 2011, seeing as milrinone is about 30 times as potent as inamrinone, and is free from thrombocytopenia side-effects. The bipyridines are characterised by two benzene rings, in which the position of one carbon is taken by a nitrogen atom. Thus, milrinone and inamrinone are a 3,4-bipyridine, whereas 2,2-bipyridine is a precursor for Diquat, and 4,4-bipyridine is the precursor for Paraquat.



Inamrinone – also a 3,4 bipyridine



Paraquat: a 4,4 bipyridine



Diquat: a 2,2 bipyridine

Inamrinone is now discontinued, and as both of the other bypiridines are hideously toxic, we will spend little time discussing them.

Milrinone lactate is available in Australia as Primacor, and comes in 10ml ampoules each containing 10mg of active ingredient. Dextrose, lactate and bicarbonate are present, acting to adjust the pH to a sour 3.2-4.0.

Administration and absorption

Milrinone is typically seen in the ICU as an infusion, with a set rate of administration. Our homestyle recipe is 20mg in 100ml, giving 200mcg per ml. Even though it comes with some glucose in the ampoule, one can actually dilute it with saline if one so wishes.

A loading dose is generally suggested - the PI suggests 50mcg/kg over 10 minutes, or 3500mcg for a 70kg person - 17.5ml of the homestyle dilution. Thereafter, one continues with a maintenance infusion. However, the rapid loading dose can play havoc with one's blood pressure, and many omit this bolus, preferring to gradually observe the effects of the infusion.

The infusion is titrated to haemodynamic effects, like the other inotropes, but this occurs within a certain range of doses - specifically, one tries to give no more than 1.13mg/kg within any given 24 hr period. That equates to 0.75mcg/kg/min, or 45mcg/hr. With the above-described standard dilution, for a 70kg person this maximum dose is about 15ml/hr.

What if I tried to drink it?

You would be among many. There was at one stage a brief era of enthusiasm for the use of milrinone in outpatient cardiology. Surely, they thought, if it is so effective in the CCU, why cant we give it to people orally and expect the same improvement in cardiac output? It must have seemed very attractive, to have all these NYHA grade IV patients walking around with newfound vigour.

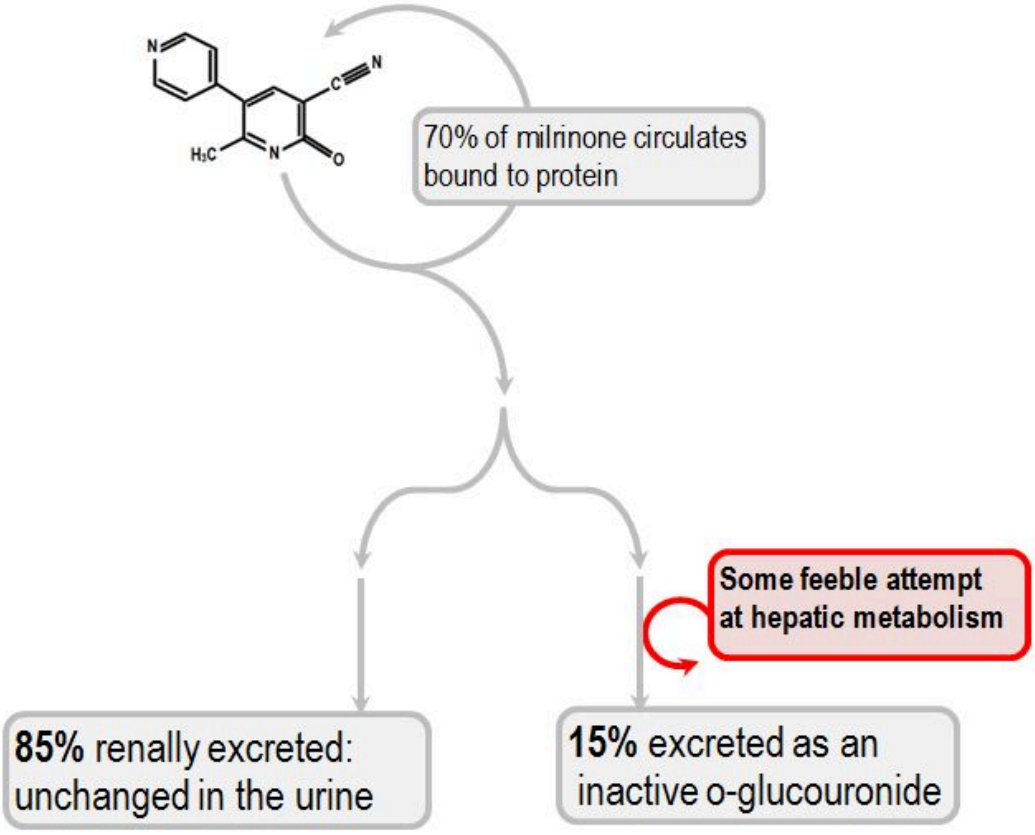
Furthermore, unlike the catecholamine inotropes, milrinone has good oral bioavailability. After eating some milrinone, healthy volunteers seemed to get about 92% of the dose into their bloodstream.

So you might ask- why have I, in the 21st century, not seen any cardiology patients with milrinone tablets on their charts? (In case you are wondering, the dose would be 10mg po qid).

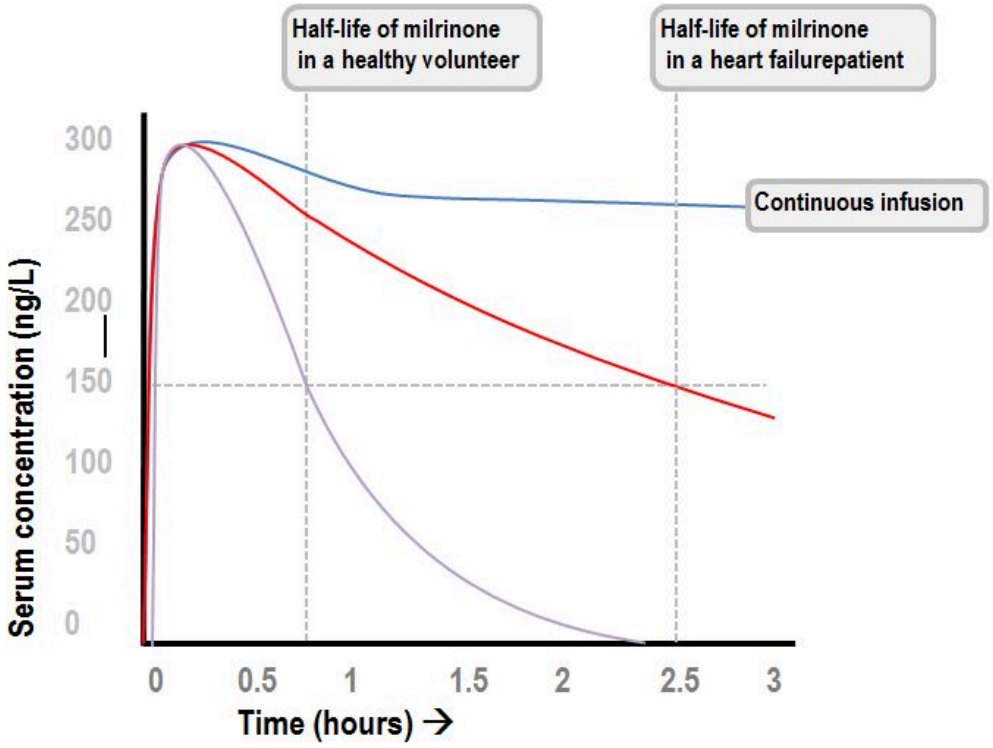
Well. Turns out, oral milrinone is horribly toxic when used in this setting - in this NEJM paper the increase in all-cause mortality was 28%.

Metabolism and Clearance

Unlike the short-lived catecholamines which get shredded by MAO and COMT, milrinone is a persistent molecule with a long halflife. The pharmacokinetics of infusion have been well described. Its volume of distribution is 0.4-0.5L/kg; given that it is about 70% protein-bound this suggests that it is essentially confined to the extracellular fluid volume.



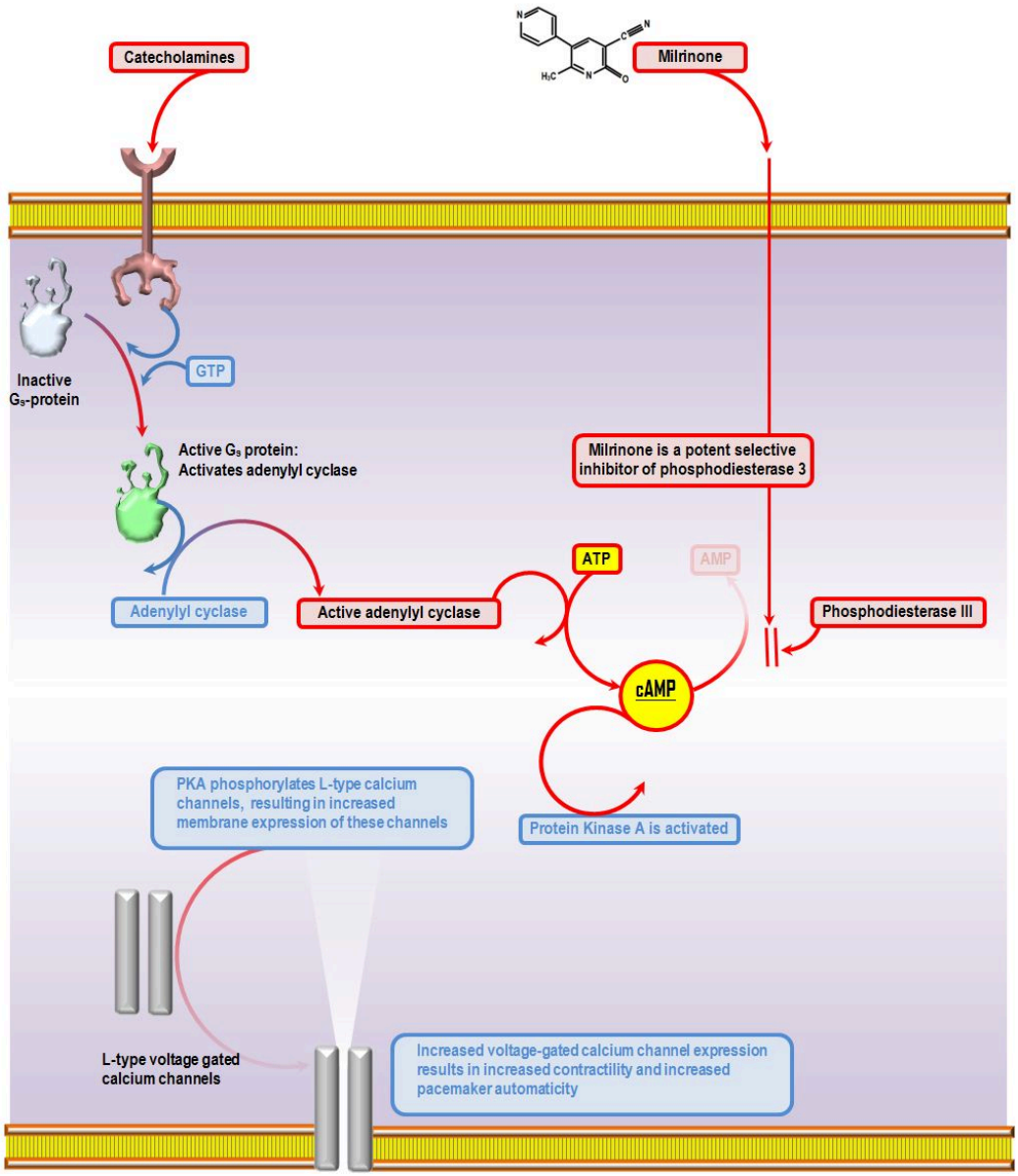
In the bloodstream, milrinone is fairly inert as far as metabolism goes. Of the free fraction, some undergoes hepatic metabolism into an inactive o-glucouronide, and the rest is excreted unchanged at a rate which varies depending on renal blood flow.



Certainly, healthy volunteers seem to pee it out at a fantastic rate, with a half-life of 0.8hrs - but when are healthy volunteers ever going to be in your ICU? Rather, heart failure patients are the normal destination for a dose of milrinone, and in these people the half-life is closer to 2.0-2.5 hrs.

Intracellular pharmacodynamics of milrinone

Milrinone is a potent selective inhibitor of phosphodiesterase 3, one of the enzymes which breaks down cAMP. The inotropic effects (and all the adverse effects) stem from the resulting increase in cAMP. In this, it is synergistic with the catecholamines.

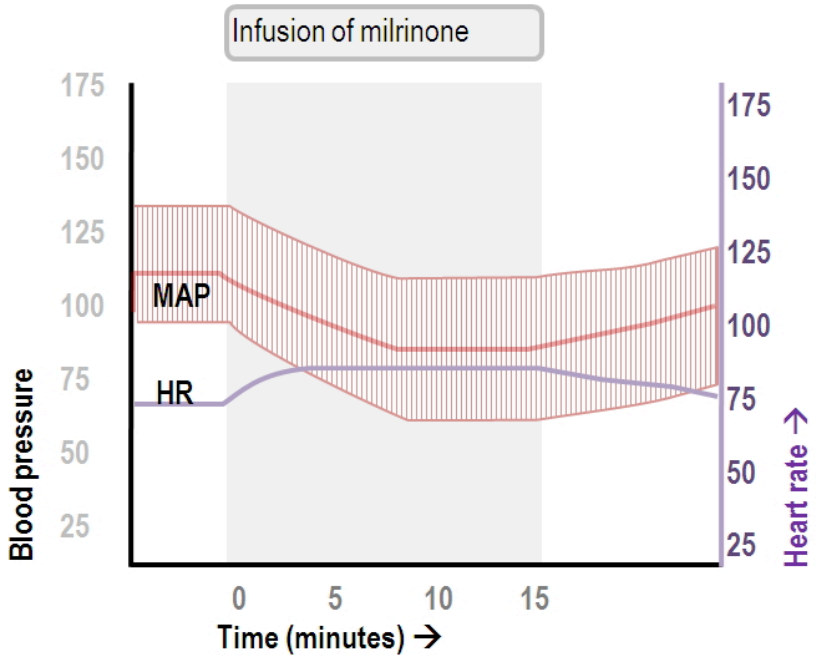


This contrasts with the inhibitors of phosphodiesterase 5 (like sildenafil), which act primarily on inhibiting the breakdown of cGMP, leading to the relaxation of vascular smooth muscle.

Milrinone demonstrates some considerable selectivity for cardiac, vascular and platelet phosphodiesterase 3.

Haemodynamic effects of milrinone

One can summarise the effects of milrinone via a stylised graph. Again, this is done by an idiot, in the dark. No graphs from early studies of the haemodynamic effects of this drug are available to me, and the graph below has been pieced together from whatever papers are available as free full text.



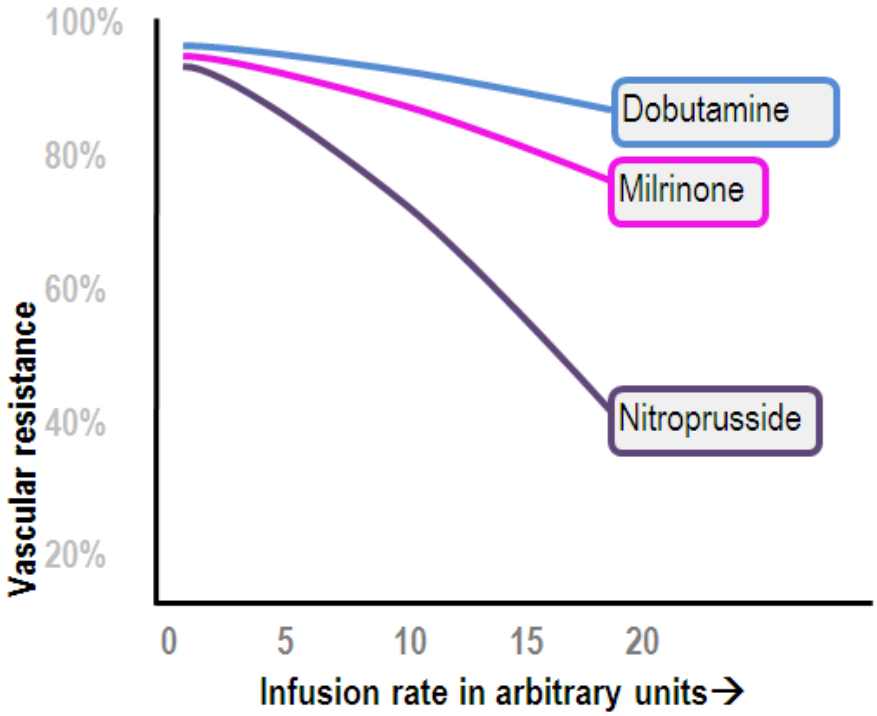
Essentially, when compared to other vasopressors and inotropes, its effect is slower in onset, and significantly slower in offset. The long halflife makes it less titratable.

Milrinone as an arterial vasodilator is more potent than dobutamine

Some investigators managed to convince a series of 13 CCF patients to undergo intra-arterial milrinone injections in 1991, to compare the effects of milrinone and a "proper" hardcore vasodilator, nitroprusside.

This article comes complete with a beautiful diagram of an arm, trussed up with a brachial arterial infusion pump. Milrinone was squirted into the brachial artery, and forearm blood flow was measured by venous occlusion plethysmography, which (when the MAP is divided by blood flow) yielded a result for vascular resistance.

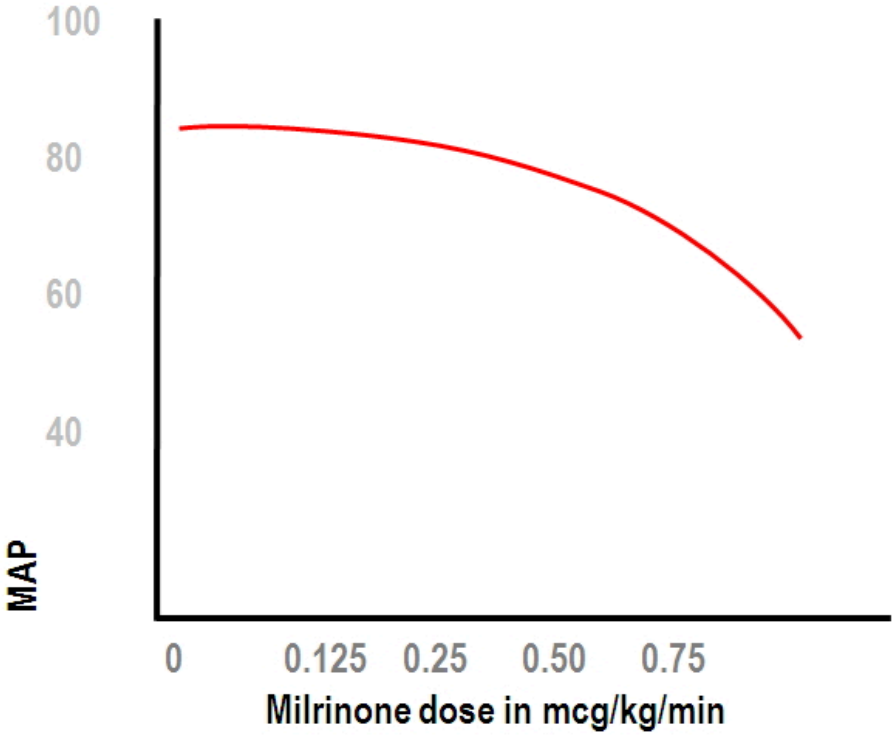
Others have also compared the haemodynamic effects of milrinone and dobutamine, to determine which has the more profound effect on blood pressure.



So, though milrinone is not quite the king of vasodilation as sodium nitroprusside is, it still causes more of a decrease in systemic vascular resistance than racemic dobutamine. This vasodilation is probably responsible for the differences in myocardial oxygen consumption between dobutamine and milrinone (i.e. unlike dobutamine, milrinone seems to have little effect on myocardial oxygen consumption while increasing cardiac output.

Of course, we rarely admit isolated forearms into the ICU. One might rightly ask, how does this vasodilation look in the living human organism? There is some data available to inform our dose decisions, though it is not entirely realistic. In a study of CCF patients, NYHA grade III and IV patients were exposed to a sudden bolus of milrinone, rather than to a gentle infusion (as is presently the standard). In any case, this is a good paper, as it also graphs some dose-response

relationships for milrinone, including esoteric left ventricular function parameters such as peak positive d*P*/d*t*.



Noticeably, there is a failure for blood pressure to budge when the milrinone dose is low. The reason for this will be revealed in a section below, when a discussion of its inotropy takes place. In a nutshell, the increase in cardiac output due to increased contractility compensates for a loss of peripheral vascular resistance, and the MAP remains more or less the same. However, as the dose increases, the vasodilation effect becomes more pronounced.

Milrinone as a venous vasodilator

Well, the general impression that milrinone is a venodilator has led to it being trialled as an agent to decrease CVP for living donor hepatectomy (and it was successful) - however: the most likely explanation for this is the increased lusitropy of the right ventricle, rather than some sort of direct effect on venous smooth muscle.

The ventricle, relaxing better and therefore filling more in diastole, increases its cardiac output, and thereby achieved a greater rate of central venous blood removal.

So, does milrinone actually act on the venous smooth muscle? There has been investigated in a Japanese dog model. The response of systemic capacitance

vessels to milrinone was interrogated; and it indeed appeared to be a venodilator. However, the intrinsic venodilatory effect was modified by the baroreflex: it seems animals with an intact sympathetic nervous system will maintain a workable CVP in spite of milrinone.

Unfortunately, unlike with noradrenaline, I was unable to find any studies where milrinone was droppered directly onto raw pieces of vein. One can imagine that the little vein pieces would melt nicely into little relaxed puddles of completely atonic smooth muscle.

Milrinone as a pulmonary vasodilator is superior to dobutamine

A lot of good evidence exists that milrinone is a potent pulmonary vasodilator.

Interest in this phenomenon led some investigators to inject it into the right pulmonary arteries of several newborn lambs. A dose-related decrease in pulmonary vascular resistance was observed. It did not take long for researchers to apply this to the adult humans.

There is one particularly good study of this effect in the human, and it arrives from a familiar setting. The adult post-CABG patients with pulmonary hypertension were treated with milrinone. In these people, after a bolus dose of 50mcg/kg the infusion maintained a mean pulmonary arterial pressure 15% lower than pre-infusion; furthermore, this effect gets larger and larger over the course of the infusion, and peaks after 12 hours - when the pulmonary vascular resistance has decreased by 30-40%.

In this effect, milrinone is superior to dobutamine. A comparison of haemodynamic effects of the two drugs has revealed a definite advantage in favour of milrinone; pulmonary arterial pressure decreased by 14% for milrinone, but only by 3% for dobutamine.

Effects of milrinone on coronary arterial flow

Given the effects of milrinone on systemic vascular resistance, it should come as no surprise that milrinone is a potent coronary vasodilator. At least in the dog model, it seems to exert this effect by the direct vasodilating effect on the vasculature of the heart. Some say this is a useful balance with its increase in cardiac contractility, as the improved coronary blood flow matches the increased demand. And of course the systemic vasodilation decreases left ventricular

afterload, thereby compensating for the increase in inotropy; this is probably why milrinone does not seem to increase the myocardial oxygen consumption even as it increases the cardiac output.

Not only that, but it seems to increase blood flow though coronary artery bypass grafts as well. Of course, this was established first by marinading donated human arteries in milrinone.

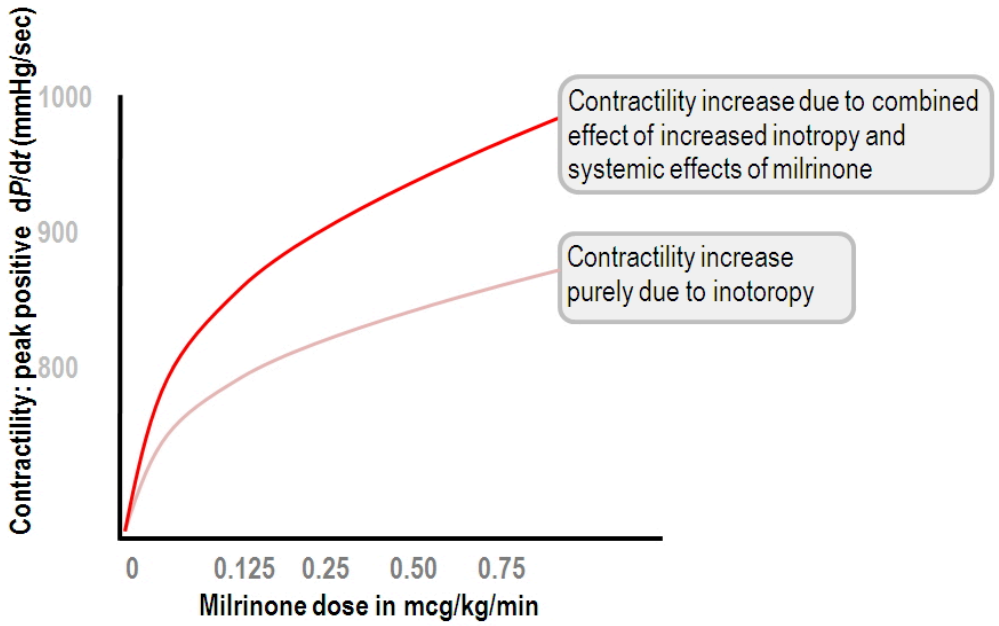
Effects of milrinone on inotropy

Milrinone seems to increase cardiac index to at least the same extent as a reasonably equivalent dose of dobutamine. A previously quoted paper demonstrated that a medium dose of milrinone (0.50mcg/kg/min) tends to increase the cardiac index from 1.7 to 3.0 L/min/m^2.

The pure inotrope and chronotrope components of milrinone are hard to separate from its effect on the peripheral circulation and on the pulmonary vessels. Anything that decreases the resistance of those vascular beds is going to improve the cardiac index. However, there is another article, which cleverly separates the inotropic effects of milrinone from their systemic effects by injecting the milrinone directly into the left main coronary artery.

What happens when you do that? Well, it seems the most significant surrogate measure of cardiac output is the peak positive dP/dt, the rate of increase of systolic pressure and thus the velocity of myocardial contraction. This measure is a good surrogate answer for the vague question "how *hard* is my ventricle pumping?".

And it turns out milrinone increases it by 30-40% at a dose of about 0.66 mcg/kg/min. Moreover, this is not a linear relationship - a low-dose milrinone infusion will increase the dP/dt by a considerable degree, and the relationship becomes more linear with increasing doses (Jaski et al, 1985)



Weirdly, this same study found that when it is injected into the coronary arteries, milrinone actually does nothing to the heart rate, or even decreases it. This suggests that the increase in heart rate is purely due to a compensatory response to vasodilation and hypotension.

Effects of milrinone on myocardial oxygen demand

Milrinone and dobutamine seem to be equivalent in increasing cardiac index, but milrinone does so without increasing myocardial oxygen consumption, likely because it also decreases afterload (and thus ventricular workload). The evidence for this is an essentially unchanged trans coronary arterio-venous oxygen difference, in the face of an increased cardiac output - essentially, you get extra cardiac output without having to pay for it with oxygen, an "increased myocardial efficiency".

Dobutamine, in contrast is nowhere near as good at decreasing afterload, because compared to milrinone it is a feeble vasodilator.

Effect of milrinone on cerebral blood flow and intracranial pressure

So, you say; this vasodilator - how will it influence my cerebral perfusion? Will there be an increased cerebral blood flow? How might a patient with a subarachnoid haemorrhage respond, with their impaired cerebral blood flow autoregulation?

Well, it certainly has been thought about before. For instance, a paper in Stoke from 2008 raves happily about the effectiveness of direct intra-arterial milrinone on cerebral vessels following post-SAH vasospasm. According to this 22-patient series, intraarterial milrinone resulted in 53±37% increase in arterial diameter. When not being infused directly into coronary arteries, milrinone still improves flow in the middle cerebral artery as a part of its systemic vasodilating effects.

Indications for use

Milrinone in cardiogenic shock

This condition is hideous and in spite of the advent of PCI, it still commands a staggering mortality rate, decreasing from about 60% to about 40% in the post-PCI era. Typically, drugs are not evaluated on their own in this condition. Indeed, papers which discuss the question "which drug is best" tend to lump all the inodilators together into the same category, and observe whether that category performs well.

Indeed, one such paper compares "inodilators" (milrinone, dobutamine, levosimendan) with "inopressors" (adrenaline, dopamine, noradrenaline). It arrives at the conclusion that mortality in cardiogenic shock is better with a combination of inopressor and inodilator.

One might become enraged at this lack of granularity. ICU is nothing if not meticulous attention to detail, and an informed choice of inotrope is exactly the sort of detail I would view as important. Certainly important enough to address in detail, to have some rational explanation as to who in one case I might use milrinone, and in another I might use dobutamine, or adrenaline, or levosimendan for that matter.

Furthermore, there is a wealth of historical inertia, which is derived mainly from the experience of various hoary elders. For instance, the ubiquity of milrinone in the cardiothoracic ICU is not matched in the general ICU, even though the same senior staff might rotate through these units. Why would this be the case?

Well. There are some scenarios in which milrinone might be the natural favourite.

Milrinone for cardiogenic shock following on-pump cardiac surgery

In this instance, we are discussing the low-cardiac-output shock state which develops in people who have recently enjoyed the experience of cardiopulmonary bypass. The trouble is their greatly diminished sensitivity to beta-1 agonists. These degenerate myocardia are desensitised chronically - a chronically failing ventricle may be 50% less responsive to beta-agonists. Not only that, but the very bypass process tends to cause a downregulation of catecholamine receptors.

It therefore stands to reason that milrinone might be a good choice for this setting. But, is there evidence to back this up? A comparison of dobutamine and milrinone in post-cardiac-surgery patients has demonstrated that when it comes to haemodynamic gains, they are about the same. The comparison was complicated somewhat by the authors' decision to destandardise the doses- the milrinone group was free to increase from 0.50 to 0.75mcg/kg/min, and the dobutamine group was free to double their dose from 10 to 20 mcg/kg/min.

In this randomised open-label trial, dobutamine actually performed a little better as an inotrope - increasing cardiac output by 55%, compared to milrinone (36%). However, this dobutamine-led victory was at a cost of increased myocardial oxygen consumption, and the difference between the two drugs can be explained entirely by the dobutamine-associated increase in heart rate. Milrinone, however, achieved its increase of cardiac output by increasing myocardial efficiency. PAWP also decreased more in the milrinone group. Mean pulmonary arterial pressure was also decreased more in the milrinone group, suggesting that the patients with severe pulmonary hypertension might not get the maximum benefit from dobutamine. This article has a series of excellent bar graphs which demonstrate the different magnitudes of the haemodynamic effects of milrinone and dobutamine - effects on PAWP, MAP, stroke volume indices, etc.

And what about off-pump bypass patients? Recent data from Iran has demonstrated that milrinone is at least somewhat better than placebo, which is comforting.

Milrinone for cardiogenic shock with diastolic heart failure

Like dobutamine, milrinone is lusitropic - i.e. it causes the myocardium to relax more between contractions, thereby increasing the potential for diastolic filling. Certainly, in 1984 people were all very excited about this, particularly as studies found "consistent and sustained improvements towards normal" in multiple indices of left ventricular diastolic function. These days, levosimendan seems to

have overtaken the old inodilators as the new popular thing. But, spare a thought for poor old milrinone, especially as it comes at a fraction of the cost.

Contraindications

Renal failure is probably the main contraindication to the use of milrinone (or rather, a caution to be moderate with one's dose). One ought to reconsider it if one is pregnant or lactating; but I suppose the counter-argument would be that having an expectant mother in poorly managed cardiogenic shock is also bad for the foetus.

Interactions

Having little involvement with the metabolic systems of the body, milrinone has few interactions. However, one should probably mention Riociguat - the only drug in Micromedex which is listed as having a significant interaction with milrinone. Apparently, it is a stimulator of soluble guanylate cyclase, which (in combination with milrinone) would cause catastrophic vasoplegia and haemodynamic collapse.

Toxicity

Well, all cardiotonic agents have some degree of cardiac toxicity. And (weirdly) they seem to have some skeletal muscle toxicity as well, at least in the soleus of the experimental rat. The toxicity tends to manifest itself as necrosis of the myocytes, similar to the histological findings in the myocardia of patients who had died of pheochromocytoma.

In overdose, however, milrinone tends to result in hypotension. An article from 2002 (which is not available to me) hints at the fact that vasopressin and noradrenaline are useful in treating this hypotension.

Of course it would be amiss not to mention the tendency towards increased mortality among ambulant heart failure patients on oral milrinone, who die (we

think) of arrhythmias.

Previous chapter: Dobutamine

Next chapter: Vasopressin

References

Sanofi prescribing information pamphlet for Primacor

Wojtczak, A., and V. Cody. "Structure-activity relationships of inotropic bipyridines: crystallographic analysis of four milrinone analogues." *Acta Crystallographica Section B: Structural Science* 51.6 (1995): 981-986.

Stroshane, Ronald M., et al. "Oral and intravenous pharmacokinetics of milrinone in human volunteers." *Journal of pharmaceutical sciences* 73.10 (1984): 1438-1441.

Packer, Milton, et al. "Effect of oral milrinone on mortality in severe chronic heart failure." *New England Journal of Medicine* 325.21 (1991): 1468-1475.

Marvellously, the journal Circulation had an entire issue devoted to the bipyridine inotropes. I expect this 1986 issue is on everybody's bedside shelf.

Edelson, J., et al. "Pharmacokinetics of the bipyridines amrinone and milrinone."*Circulation* 73.3 Pt 2 (1986): III145.

Alousi, A. A., and D. C. Johnson. "Pharmacology of the bipyridines: amrinone and milrinone." *Circulation* 73.3 Pt 2 (1986): III10.

Benotti, Joseph R., et al. "Pharmacokinetics and pharmacodynamics of milrinone in chronic congestive heart failure." *The American journal of cardiology* 56.10 (1985): 685-689.

Masaaki, Ito, et al. "Selective inhibition of cyclic AMP phosphodiesterase from various human tissues by milrinone, a potent cardiac bipyridine." *Biochemical pharmacology* 37.10 (1988): 2041-2044.

Cody, ROBERT J., et al. "Identification of the direct vasodilator effect of milrinone with an isolated limb preparation in patients with chronic congestive heart failure." *Circulation* 73.1 (1986): 124-129.

Grose, Richard, et al. "Systemic and coronary effects of intravenous milrinone and dobutamine in congestive heart failure." *Journal of the American College of Cardiology* 7.5 (1986): 1107-1113.

Ryu, H-G., et al. "Low central venous pressure with milrinone during living donor hepatectomy." *American Journal of Transplantation* 10.4 (2010): 877-882.

Jaski, Brian E., et al. "Positive inotropic and vasodilator actions of milrinone in patients with severe congestive heart failure. Dose-response relationships and comparison to nitroprusside." *Journal of Clinical Investigation* 75.2 (1985): 643.

Ludmer, P. L., et al. "Separation of the direct myocardial and vasodilator actions of milrinone administered by an intracoronary infusion technique." *Circulation* 73.1 (1986): 130-137.

Hirakawa, Senri, et al. "Effects of milrinone on systemic capacitance vessels in relation to venous return and right ventricular pump function." *Journal of cardiovascular pharmacology* 19.1 (1992): 96-101.

Evans, Dale B. "Overview of cardiovascular physiologic and pharmacologic aspects of selective phosphodiesterase peak III inhibitors." *The American Journal of Cardiology* 63.2 (1989): A9-A11.

Coe, J. Y., et al. "Bipyridine derivatives lower arteriolar resistance and improve left ventricular function in newborn lambs." *Pediatric research* 22.4 (1987): 422-428.

Harris, M. N., A. K. Daborn, and J. P. O'Dwyer. "Milrinone and the pulmonary vascular system." *European journal of anaesthesiology. Supplement* 5 (1992): 27.

Feneck, Robert O., et al. "Comparison of the hemodynamic effects of milrinone with dobutamine in patients after cardiac surgery." *Journal of cardiothoracic and vascular anesthesia* 15.3 (2001): 306-315.

Liu, James J., et al. "Direct vasodilator effect of milrinone, an inotropic drug, on arterial coronary bypass grafts." *The Journal of thoracic and cardiovascular surgery* 113.1 (1997): 108-113.

García-Rinaldi, Raul, et al. "Intraluminal milrinone for dilation of the radial artery graft." *Texas Heart Institute Journal* 26.3 (1999): 189.

Grose, Richard, et al. "Systemic and coronary effects of intravenous milrinone and dobutamine in congestive heart failure." *Journal of the American College of Cardiology* 7.5 (1986): 1107-1113.

Baim, Donald S. "Effect of phosphodiesterase inhibition on myocardial oxygen consumption and coronary blood flow." *The American journal of cardiology* 63.2 (1989): A23-A26.

Kabela, E., L. Barcenas, and A. Farah. "The effects of milrinone (Win 47203) on the coronary blood flow and oxygen consumption of the dog heart-lung preparation." *American Heart Journal* 111.4 (1986): 702-709.

Ludmer, P. L., et al. "Separation of the direct myocardial and vasodilator actions of milrinone administered by an intracoronary infusion technique."*Circulation* 73.1 (1986): 130-137.

Monrad, E. Scott, et al. "Effects of milrinone on coronary hemodynamics and myocardial energetics in patients with congestive heart failure." *Circulation* 71.5 (1985): 972-979.

Fraticelli, Amanda Tarabini, et al. "Milrinone for the treatment of cerebral vasospasm after aneurysmal subarachnoid hemorrhage." *Stroke* 39.3 (2008): 893-898.

Sulek, Cheri A., Mark L. Blas, and Emilio B. Lobato. "Milrinone increases middle cerebral artery blood flow velocity after cardiopulmonary bypass."*Journal of cardiothoracic and vascular anesthesia* 16.1 (2002): 64-69.

Pirracchio, Romain, et al. "The Effectiveness of Inodilators in Reducing Short Term Mortality among Patient with Severe Cardiogenic Shock: A Propensity-Based Analysis." *PloS one* 8.8 (2013): e71659.

Jebeli, Mohammad, et al. "Effect of milrinone on short-term outcome of patients with myocardial dysfunction undergoing coronary artery bypass

graft: A randomized controlled trial." *Cardiol J* 17.1 (2010): 73-78.

Bristow MR, Ginsburg R, Minobe W et al. Decreased catecholamine sensitivity and beta-adrenergic-receptor density in failing human hearts. N Engl J Med, 1982; 307: 205–211.

Schwinn DA, Leone BJ, Spahn DR et al. Desensitization of myocardial beta-adrenergic receptors during cardiopulmonary bypass. Evidence for early uncoupling and late downregulation. Circulation, 1991; 84: 2559–2567.

Feneck, Robert O., et al. "Comparison of the hemodynamic effects of milrinone with dobutamine in patients after cardiac surgery." *Journal of cardiothoracic and vascular anesthesia* 15.3 (2001): 306-315.

Hadadzadeh, Mehdi, et al. "Effect of Milrinone on Short Term Outcome of Patients with Myocardial Dysfunction Undergoing Off-Pump Coronary Artery Bypass Graft: A Randomized Clinical Trial." *Acta Medica Iranica* 51.10 (2013): 681-686.

Yano, Masafumi, et al. "Effect of milrinone on left ventricular relaxation and Ca2+ uptake function of cardiac sarcoplasmic reticulum." *American Journal of Physiology-Heart and Circulatory Physiology* 279.4 (2000): H1898-H1905.

Monrad, E. S., et al. "Improvement in indexes of diastolic performance in patients with congestive heart failure treated with milrinone." *Circulation* 70.6 (1984): 1030-1037.

Burniston, Jatin G., et al. "Relative toxicity of cardiotonic agents."*Cardiovascular toxicology* 5.4 (2005): 355-364.

Baer, A. B., and C. P. Holstege. "Milrinone overdose induced hypotension reversed by vasopressin and norepinephrine infusions." *J Toxicol Clin Toxicol*40.5 (2002): 690. - only available as a citation!

[Submit a comment or correction]

© Alex Yartsev
2013-2025